AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
Formerly The American Fertility Society

November 1, 2005

BY ELECTRONIC MAIL

Division of Dockets Management
United States Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2005N-0345 — *Drug Approvals: Circumstances In Which An Active Ingredient May Be Simultaneously Marketed In Both A Prescription Drug Product And An Over-The-Counter Drug Product*

Dear Madam:

On September 1, 2005, the Food and Drug Administration ("FDA") issued an Advanced Notice of Proposed Rulemaking ("ANPR") in connection with its recent decision to delay approval of Barr Laboratories' emergency contraception ("EC") product, Plan B (levonorgestrel), for over-the-counter ("OTC") use in women sixteen and older. Several days earlier, FDA had announced that it was unable to reach a decision on Barr's proposal, contained in a supplemental New Drug Application ("sNDA"), to "switch" the drug from prescription-only to OTC because of the "novel regulatory issues" posed by the simultaneous marketing of a product for prescription and OTC use. *See* FDA Statement, FDA Takes Action on Plan B: Statement by FDA Commissioner Lester M. Crawford (Aug. 26, 2005) *at* www.fda.gov/bbs/topics/news/2005/NEW01223.html.

The American Society for Reproductive Medicine ("ASRM") would like to take this opportunity to comment on the issues raised in the ANPR. Specifically, the regulatory framework governing drug approvals and prescription-to-OTC "switches" are clear and should lead to swift approval of Barr's sNDA. The Federal Food, Drug, and Cosmetic Act ("FDCA") establishes a standard for classifying a drug as prescription-only that allows the agency to impose age requirements on prescription use. Moreover, FDA has ample legal authority to enforce such a restriction and has done so with respect to at least one other product, an "adults only" Nicorette (nicotine polacrilex) gum. Consequently, FDA should stop this unreasonable delay and grant approval of OTC levonorgestrel.

I. BACKGROUND

Plan B was approved on July 28, 1999, under a new drug application ("NDA") submitted by the Women's Capital Corporation and subsequently purchased by Barr. The NDA referenced clinical data on nearly 15,700 women who had used levonorgestrel for EC from a study conducted by investigators working under the sponsorship of the World Health

Organization and World Bank Special Programme of Research, Development and Research Training in Human Reproduction. *See* NDA No. 21,045, FDA Medical Officer Review, Levonorgestrel 0.75mg for Emergency Contraception (June 23, 1999).

In February 2001, ASRM joined over sixty organizations in filing a citizen petition seeking a switch from prescription to OTC status for Preven Emergency Contraceptive Kit (ethinyl estradiol; levonorgestrel) and Plan B. *See* Docket No. 2001P-0075. On several occasions since then, ASRM has communicated its view concerning the safety and effectiveness of Plan B to President Bush, then-Commissioner Mark McClellan, Secretary of HHS Tommy Thompson, and FDA's Reproductive Health Drugs Advisory Panel.[1] Briefly, ASRM has stated that:

- EC is difficult to obtain during the weekend, and emergency rooms do not always provide EC. Access to EC is crucial if it is to work effectively.
- To optimize women's health, impediments to obtaining EC should be removed; OTC availability of EC would result in increased use which could prevent 1.7 million unplanned pregnancies per year and countless abortions.
- Five states have already made it available directly from pharmacists without prescription.
- Studies show the drug is safe and that consumers are easily able to follow package instructions.
- Use of EC will not influence consumers to use regular contraception less frequently; if EC is available OTC, they are more likely to use it when necessary.

On April 16, 2003, Women's Capital Corporation filed a prescription-to-OTC switch application with FDA. *See* www.barrlabs.com. In December 2003, FDA convened a Joint Meeting of the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs (the "Joint Committee") to consider the proposed switch. The Joint Committee voted 23-4 that Plan B should be switched to OTC status.

At least one senior FDA official reviewed data contained in the Barr sNDA and concluded that it is adequate to support approval. On April 22, 2004, Director of New Drugs Dr. John K. Jenkins wrote a memo to the NDA concluding that, "[i]n my opinion, these studies provide adequate evidence that women of childbearing potential can use Plan B safely, effectively, and appropriately for emergency contraception in the non-prescription setting." *See* Memorandum from John K. Jenkins, MD, Director, Office of New Drugs, FDA to NDA 21-045 (Apr. 22, 2004).

Nevertheless, several days later, FDA notified Barr that its supplemental application for OTC status was not approvable because Barr had not provided adequate data to

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[1] ASRM submitted comments to Docket No. 2001P-0075 on July 29, 2005 and December 8, 2003.

demonstrate that Plan B can be used safely by young adolescent women without the professional supervision of a practitioner licensed by law to administer the drug. *See* Letter to Barr from Steven Galson (May 6, 2004) (available at http://www.barrlabs.com/pages/nprpr.html). FDA commented that only 29 of the 585 subjects enrolled in the study were 14-16 years of age, and none was under 14 years of age. FDA noted concerns from some members of the Joint Committee that actual use data did not reflect the overall population of non-prescription users, particularly given the small sample of younger age groups.

In July 2004, Barr submitted a revised sNDA seeking approval of OTC Plan B for women 16 years of age and higher. On August 26, 2005, FDA issued a letter to Barr stating that the agency was unable to make a determination on the approvability of the sNDA,[2] and, on September 1, issued the ANPR, which sets out several legal issues for comment. ASRM is deeply disappointed by the agency's repeated delay in approving Plan B for over-the-counter use, and submits these comments in response to the agency's request.

II. DISCUSSION

A. FDA's Legal Authority is Clear and Supports Approval

No statutory provision prevents FDA from imposing an age limitation on the prescription drug status of a new drug. As a fundamental matter, the FDCA presumes that a new drug may be available OTC unless it falls within the definition of a prescription drug in Section 503(b) of the Act. 21 USC 353(b). *See, e.g.*, 21 CFR 330.10(a)(4)(vi); *see also* Leg. Hist. of Durham-Humphrey Act at S. Rep. No. 946, at 1951 USCCAN 2454, 2461. Section 503(b) provides that FDA shall impose a prescription-only restriction where a new drug

> because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug.

Thus, the statute allows FDA to determine, based either on the data contained in the sNDA or the lack of necessary data, that Plan B poses a "potential for harmful effect" if used in women under age 16. FDA could also find that "collateral measures" are necessary for its safe use by women under age 16 — namely that distribution be limited to circumstances where a licensed practitioner is available to supervise its use.[3]

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[2] According to Barr, the letter states that FDA "has completed its review of this application, as amended, and has concluded that the available scientific data are sufficient to support the safe use of Plan B as an OTC product . . . for women who are 17 years of age and older." *See* www.barrlabs.com.

[3] Indeed, the statute is silent with respect to whether age is a relevant factor when interpreting and applying section 503(b). Thus, under settled legal principles, the agency may "fill the gaps" in the statute through reasonable

FDA has published regulations governing OTC drugs. In considering whether to allow a drug to be available OTC through publication of a drug monograph, the agency considers established factors — safety and effectiveness, the benefit-to-risk ratio, and whether clear and understandable labeling can be written for self-medication without the intervention of a health professional. *See* 21 CFR 330.10(a)(4). Similarly, when considering whether a prescription drug should "switch" to OTC status, the agency considers related factors such as a consumer's ability to self-diagnose and self-treat, the incidence of side effects and adverse events, the potential for misuse, and whether the drug's use might mask more serious conditions that require medical attention. As ASRM has repeatedly asserted, these factors strongly support approval of OTC Plan B.

In fact, since Barr filed its application, two studies have been published that address certain of these factors. Most recently, the *British Medical Journal* published the results of a survey study of approximately 7600 women aged 16-49 finding that nonprescription availability of EC in the United Kingdom did not lead to an increase in unprotected sex, an increase in the use of EC, or a decrease in "more reliable methods of contraception." Marston, et al., Impact On Contraceptive Practice Of Making Emergency Hormonal Contraception Available Over The Counter In Great Britain: Repeated Cross Sectional Surveys, 331 Brit. M.J. 271 (2005). In January 2005, the *Journal of the American Medical Association* published the results of a randomized, single-blind, controlled trial of 2117 women, aged 15 to 24 years, in which the participants either had pharmacy access to EC, advance provision of Plan B, or clinical access to EC (control group). The researchers found that access to EC through pharmacies or advance provision "did not have a detrimental effect on contraceptive use or sexual behavior." Raine et al., Direct Access to Emergency Contraception Through Pharmacies and Effect on Unintended Pregnancy and STIs, 293 JAMA 54 (Jan. 2005). This information underscores the widespread belief among women's health professionals that OTC EC would provide tremendous benefits without posing an unwarranted risk of misuse or adverse health consequences.

As the agency recognized in the September 1 ANPR, FDA has allowed marketing of the same active ingredient in products that are both prescription and OTC where "some meaningful difference exists between the two that makes the prescription product safe only under the supervision of a licensed practitioner." 70 Fed. Reg. 52050 (Sept. 1, 2005). FDA provided several examples of such drugs, and reiterated that the "key distinction" between the OTC and prescription versions of those products is "some meaningful difference between the two products," for example, "indication, strength, route of administration, dosage form." *Id.*

A drug product is approved for those uses set forth in its labeling, the scope of which is limited to specific statements about the "conditions" of its proper use — those "prescribed, recommended, or suggested" in the labeling. 21 USC 355(d)(1). Thus, labeling that includes specific limitations on the appropriate patient population for which the drug is intended

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interpretation. *See U.S. v. Mead Corp.*, 533 U.S. 218, 234 (2001); *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).

can denote a "meaningful difference" in the prescription drug and the OTC drug product.[4] Quite simply, levonorgestrel labeled for prescription use is a different drug that levonorgestrel labeled for OTC use. Indeed, as FDA acknowledges, it has approved OTC and prescription versions of a product based on differences in "indication," which constitutes a meaningful difference in the two products' intended or labeled uses.

ASRM believes that FDA has ample authority to make a similar distinction between prescription and OTC levonorgestrel and should do so immediately.

B. FDA Has Ample Authority to Enforce an Age Restriction — both as a Matter of Law and in Practice

FDA also requested comments on the enforceability of an age limitation for a product sold both by prescription and over the counter. It is important to note that FDA has approved an sNDA for an "adults only" OTC version of a prescription product — Nicorette gum. In February 1996, FDA issued an approval letter for the OTC sale of Nicorette, a smoking-cessation product, for consumers 18 years of age or older. The letter stated that Nicorette "product cartons must bear the legend: Not for sale to those under 18 years of age. Proof of age required. Not for sale in vending machines or from any source where proof of age cannot be verified." *See* Letter to Hoechst Marion Roussel, Inc. from Paula Botstein, CDER, FDA (Feb. 9, 1996) ("Nicorette Approval Letter (Feb. 9, 1996)"). We are not aware of any challenge — legal or practical — to FDA's enforcement of this restriction, nor do we foresee any difficulty in enforcing such a limitation on OTC Plan B.

1. OTC Levonorgestrel Intended for Use by Women Falling Under the Age Limitation Would be an "Unapproved New Drug"

The FDCA provides a panoply of legal restrictions on the sale of unapproved new drugs. As a matter of law, FDA can restrict the "introduction into interstate commerce" of an unapproved new drug such as OTC Plan B intended for use by a woman under the age of 16.

The statute prohibits the "introduction into interstate commerce [of] any new drug" the approval of which is not in effect under section 505 of the FDCA. 21 USC 355(a); 331(d). New drugs are approved by the agency after evaluation of the results of clinical investigations designed to demonstrate whether the drug is safe and effective "under the conditions of use prescribed, recommended, or suggested in the proposed labeling." *See* 21 USC 355(d). Any new "intended use" of the product by the manufacturer beyond the use set forth in the labeling requires "adequate directions for use," which are necessarily lacking without

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[4] In June 2005, FDA approved a drug for use only in a specific subpopulation — African Americans. The drug, BiDil® (hydralazine hydrochloride; isosorbide dinitrate), is indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients.

FDA review and approval. *See* 21 USC 352(f)(1); 21 CFR 201.5; 201.128. Promotion of OTC Plan B to women under the age of 16 would create an unapproved new drug, as would sale of the product "for a purpose for which it is neither labeled nor advertised" by persons legally responsible for its labeling. 21 CFR 201.128.

2. FDA Can Enforce An Age Limit As a Practical Matter

Moreover, FDA can enforce an age limitation through a variety of measures.

FDA routinely requests from drug applicants commitments to implement post-market surveillance and marketing plans. On approval of Nicorette, for example, the agency stipulated OTC availability for an adult-only population and requested a number of post-marketing commitments, including a surveillance study designed to identify and report on sale to or use by people less than 18 years of age. Nicorette Approval Letter (Feb. 9, 1996). FDA also recently approved a new drug with a post-marketing "risk management plan" that included a commitment that the manufacturer refrain from using direct-to-consumer advertising. Letter to Amylin Pharmaceuticals, Inc. from Robert J. Meyer, CDER, FDA (Mar. 16, 2005) (regarding FDA approval of Symlin (pramlintide acetate)). FDA could request that Barr conduct similar surveillance studies and agree to appropriate advertising limitations.[5]

Other elements of a possible post-marketing distribution commitments could include elements such as (1) limitations on "trial size" or "sample" packs; (2) use of child-resistant packaging; (3) distribution restrictions excluding channels such as convenience stores or vending machines; (4) incentives to retailers to shelve Plan B close to the pharmacy or with other OTC drugs; and (5) easy access to patient information regarding use of emergency contraception (toll-free phone number on labeling). *See* Nicorette Approval Letter (Feb. 9, 1996).

And, both Barr and FDA could cooperate with state pharmacy boards and local pharmacies to ensure enforcement of the age limitation at the point of sale. FDA has entered into memoranda of understanding ("MOUs") with state regulatory agencies to supplement investigative abilities. *See* FDA, Investigations Operations Manual, Ch. 3 (Federal-State Cooperation) *at* http://www.fda.gov/ora/inspect_ref/iom/ChapterText/330part1.html#331.02.

In short, FDA has a long record of approving drugs that pose risks to certain populations. It has attempted to address those risks through agreements with the manufacturer and other enforcement agencies so that safe and effective drug products could be made available

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[5] Recently, the Pharmaceutical Research and Manufacturers Association published voluntary principles governing direct to consumer advertising. *See* PhRMA Guiding Principles: Direct to Consumer Advertisements About Prescription Medicines (July. 2005). These establish that such advertisements "clearly indicate that the medicine is a prescription drug to distinguish such advertising from other advertising for non-prescription products." They also stress that advertisements "be targeted to avoid audiences that are not age appropriate for the message involved."

to the public. FDA assessed those risks and determined that they did not outweigh the benefits such that approval was delayed indefinitely.

Conclusion

For all these reasons, and those included in ASRM's previous submissions to Docket No. 2001P-0075, we urge FDA to approve Plan B for OTC use.

Sincerely,

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